REMARKS

Applicants have amended the specification to correct an inadvertent typographical error in the identification of the provisional application of which the instant application claims benefit. Support for the amendment appears, e.g., in Applicants' Initial Application Data Sheet.

Claims 24, 27, 29, 32, 35, 37 and 40 are canceled without prejudice or disclaimer. Claim 23 is amended to incorporate the steps of prior claims 24 and 27 and is supported throughout the specification as originally filed, e.g., page 6 line 10 to page 7, line 22. The dependency of claim 28 is amended consistent therewith. Support for amended claims 25-26 appears throughout the specification as filed, e.g., page 10, line 34 to page 11, line 14. Claim 42 is amended to correct an inadvertent typographical error.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's consideration of the Information Disclosure Statement as filed April 4, 2006.

II. The Rejection of Claims 23-28, 32-34, 38-39 and 43-44 under 35 U.S.C. 112 (Written Description)

Claims 23-28, 32-34, 38-39 and 43-44 stand rejected under 35 U.S.C. 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. This rejection is respectfully traversed.

As the Examiner correctly points out, the written description requirement necessitates that the applicant "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. See *In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976).

Moreover, the Patent Office's *Written Description Training Materials*, Revision 1 (March 25, 2008) provides guidance in applying the written description requirement. Particularly

relevant to the instant application is Example 16 "Process Claim Where Novelty Resides in the Process Steps." Example 16 provides "Claim 1" which is a claim to a method of introducing a nucleic acid into the mitochondria of mammalian cells comprising contacting a nucleic acid with compound X to form a complex of said nucleic acid and compound X; contacting mammalian cells with said complex; and incubating said sells and said complex under specific, novel conditions. The specification of Example 16 discloses the reduction to practice of only a single nucleic acid (the beta-galactosidase gene) used to transform mitochondria. The specification of Example 16 also provides the actual reduction to practice of only one species within the claimed genus, i.e., transformation of mitochondria with DNA encoding beta-galactosidase. The level of skill and knowledge in the art is such that those skilled in the art know of numerous nucleic acids that could potentially be complexed with compound X to be used in the claimed method to transform the mitochondria. Moreover, Example 16 states that although the sequences of these nucleic acids are not disclosed in the specification, a patent application is not required to reproduce knowledge that is available in the art. The degree of predictability with the claimed genus is high, because the introduction of a nucleic acid into mitochondria is disclosed to depend on complexing with compound X and contacting the complex with mammalian cells under specified conditions. As set forth in the specification, these conditions would be expected to result in transformation regardless of which nucleic acid is complexed and contacted with cells. Thus, one of ordinary skill in the art would recognize the inventor to have been in possession of the claimed method at the time of filing. The conclusion is that the written description requirement is satisfied for Claim 1 of Example 16.

The amended claims are directed to a method of screening recombinant bacterial host cells comprising a gene library for a protein secreting host cell. Just as one skilled in the art would expect the conditions of Example 16 to result in transformation of the mitochondria regardless of which nucleic acid is complexed and contacted with cells, so too would one skilled in the art expect that the instant claims would result in the identification of those bacterial host cells that efficiently secrete proteins.

Applicants were clearly in possession of recombinant bacterial host cells comprising a gene library and a secretion stress inducible promoter operably linked to a nucleic acid sequence encoding a report protein or a regulator protein. The specification provides teachings on the host cell, secretion stress inducible promoters, reporter proteins and nucleic acid sequences useful according to the claimed invention. See, e.g., page 6, line 25 to page 13, line 10. The specification also provides instructions on manipulating the nucleic acid sequences of

a library, as well as guidance on the nucleic acid constructs, expression vectors and transformation useful therefor. See, e.g., page 13, line 12 to page 18, line 14. The specification further provides guidance on the secretion of enzymes according to a particular embodiment of the invention. See, e.g., page 18, line 16 to page 26, line 14. The specification also provides guidance on the methods of production for culturing the transformed or transfected host cells and selecting recombinant host cells according to the desired level of reporter gene activity. See, e.g., page 26, line 16 to page 27, line 27. The Examples as filed provide further evidence of Applicants' possession of the claimed invention. For example, Example 2 provides the secretion stress based screening of a library in Bacillus, and demonstrates library construction and the identification and isolation of eight clones expressing and secreting large amounts of recombinant protein from a total number of 16,000-20,000 transformants, while Example 3 provides secretion stress based screening of a non-cult genomic DNA library in Bacillus. See, e.g., page 32, line 19 to page 36, line 20.

Thus, those skilled in the art would have recognized Applicants' specification as filed as showing that Applicants were in possession of the claimed genus at the time of filing. Applicants submit that the specification provides an adequate written description of the claimed invention.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112, first paragraph (written description). Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 25-26, 29, 35, 37 and 40 under 35 U.S.C. 112 (Indefiniteness)

Claims 25-26, 29, 35, 37 and 40 stand rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite. This rejection is respectfully traversed.

The Examiner contends that claims 29, 35, 37 and 40 are indefinite in the recitation of certain claim terms. To expedite prosecution, claims 29, 35, 37 and 40 are canceled herewith, thereby rendering moot this aspect of the rejections.

The Examiner contends that claims 25-26 are indefinite in the recitation of "wherein the regulator protein controls the express of the reporter gene" or "wherein the regulator protein is an activator or repressor of the expression of the reporter protein." Amended claims 25-26 delete these recitations, thereby obviating this aspect of the rejections.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Rejection of Claims 23-28, 39 and 43-44 under 35 U.S.C. 102

Claims 23-28, 39 and 43-44 stand rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Griffith et al, FASEB Journal, 17, No. 4-5, Abstract No. 369.8 (2003) ("Griffith Abstract") or Griffith et al., FEBS LETT. 553(1-2), pp. 45-50 (2003) ("Griffith"). Claims 23-28, 39 and 43-44 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Jones et al., Embo J., 16, pp. 6394-6406 (1997) ("Jones"). This rejection is respectfully traversed.

Griffith Abstract and Griffith both disclose monitoring the copy-number of a single known gene encoding a membrane-protein in a yeast host cell by utilizing a secretion-stress inducible promoter operably linked to a reporter (UPR-lacZ).

Jones discloses a bacterial host cell comprising one or two known genes (papG and/or papD) or a known operon (pap), where none encode secreted proteins, while monitoring a secretion-stress inducible promoter operably linked to a reporter (degP-lacZ).

In contrast, the present invention relates to a method of screening a gene library in bacterial host cells for genes encoding secreted proteins by monitoring the activity of a secretion stress inducible promoter operably linked to a nucleic acid sequence encoding a reporter protein or a regulator protein; thus indirectly indicating the presence of a recombinant gene encoding a secreted protein within the selected cell.

None of the cited references disclose all of the features and steps of the claims submitted herewith. Therefore, the amended claims are novel over Griffith Abstract, Griffith and/or Jones.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 29-38 and 40-42 under 35 U.S.C. 103

Claims 29-38 and 40-42 stand rejected under 35 U.S.C. 103 as allegedly being unpatentable over Lesley et al., Protein Eng. 15, pp. 153-160 (2002) ("Lesley") or Waldo, Curr. Opin. Chem. Biol., 7, pp. 33-38 (2003) ("Waldo") in view of Noone, J. Bacteriol., 183(2), pp. 654-663 (2001) ("Noone"). This rejection is respectfully traversed.

The present invention is directed to a method of screening recombinant bacterial host cells comprising a gene library for a protein secreting host cell, the method comprising the steps of:

providing a recombinant bacterial host cell comprising a gene library and a secretion stress inducible promoter operably linked to a nucleic acid sequence encoding a reporter protein or a regulator protein; culturing the bacterial host cell under conditions promoting expression of the gene library; and selecting a bacterial host cell which expresses the reporter protein or regulator protein.

In contrast, Lesley and Waldo relate to the expression of a few well-known non-secreted (membrane) proteins.

Noone merely discloses the secretion-stress promoters employed in the instant invention.

None of the cited references teach or suggest Applicants' claimed methods directed to isolating a gene that encodes a secreted protein from a gene library in a bacterial host cell. Thus, the cited references fail to teach or suggest all of the claim elements.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

All required fees were charged to Novozymes North America, Inc.'s Deposit Account No. 50-1701 at the time of electronic filing. The USPTO is authorized to charge this Deposit Account should any additional fees be due.

Respectfully submitted,

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